REMARKS

Status of the Claims.

Claims 1-12, and 14-17 are pending with entry of this amendment, claim 13 being cancelled and no claims being added herein. Claims 1, 2, 6, 9, 11, 15, 16, and 17 are amended herein. These amendments introduce no new matter. Support is replete throughout the specification (*e.g.*, in the claims as filed, page 42, lines 10-11, at page 7, lines 10-12, at page 12, lines 26-28, and the like).

Title of the Invention.

The Examiner objected to the specification stating that the title is not reflective of the claimed invention. The title is amended herein thereby obviating this objection.

35 U.S.C. §112, second paragraph.

Claims 1-17 were rejected under 35 U.S.C. §112, second paragraph, for the reasons described below:

A) The recitation of "CYP24" in claims 1, 2, 9-11, and 15-17.

Claims 1, 2, 9-11, and 15-17 were rejected under 35 U.S.C. §112, second paragraph, as indefinite it was allegedly unclear what type of CYP24 molecules was being referenced to in the claims. Claims 1, 2, 6, 9, 11, and 15-17 are amended herein to clarify the reference to nucleic acid or protein thereby obviating this rejection.

B) Claim 6 use of "RNA".

Claim 6 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite in the recitation of both "RNA" and "mRNA". Claim 6 is amended herein to consistently refer to "mRNA" thereby obviating this rejection.

C) Claims 7 and 10.

Claims 7 and 10 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because according to the Examiner they suggest that vitamin D receptor activity is equivalent or correlative to CYP24 mRNA and CYP24 protein. Applicants traverse.

As stated in the specification, at page 21, lines 5-

> With respect to assays based on *CYP24* "activity" level (*e.g.*, level of transcript, level of translated protein, level of protein enyzmatic activity), the close coupling of transcription of *CYP24* to vitamin D receptor (*VDR*) level and activity complicates the evaluation of *CYP24* level. **In short, *CYP24* expression levels depend on *VDR* activity as well as the magnitude of transcription resulting from copy number increases. Thus, particularly in embodiments relying on assays of *CYP24* "activity", evaluation of *CYP24* levels preferably involves measurement not only of *CYP24* levels in tumor cells relative to normal tissue, but also the *VDR* levels and activities.**

The specification thus teaches that CYP24 expression levels can depend on vitamin D receptor (VDR) activity. Accordingly, in certain embodiments, particularly when assaying CYP24 activity the invention contemplates correcting for VDR expression level or activity as recited in claims 7 and 10. When read in light of the specification claims 7 and 10 clearly define the meets and bounds of the invention and are as clear as the subject matter permits. Accordingly the requirements of 35 U.S.C. §112, second paragraph, are met and the rejection of claims 7 and 10 on these grounds should be withdrawn.

D) Claim 15.

Claim 15 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because, according to the Examiner, "it is not clear what qualitative difference between CYP24 in the biological sample versus the CYP24 in the control sample is regarded as significant." Claim 15 is amended herein to recite ". . . a statistically significant difference **at the 95 percent or greater confidence level**."

Claim 15, as amended, clearly defines what difference is regarded as significant. Accordingly the rejection of this claim under 35 U.S.C. §112, second paragraph, should be withdrawn.

35 U.S.C. §112, first paragraph, written description.

Claims 1-17 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to meet the written description requirement. According to the Examiner, the claims are drawn to a method of prognosticating cancer by detecting the level of CYP24. According to the Examiner, the acronym CYP24 3ncompases a genus of molecules that are not necessarily wild type forms of the

CYP24. The Examiner further asserted that "[a]pplicants are not in possession of the entire genus of CYP24 molecules embraced by the claim language". Applicants traverse by argument and amendment.

Claim 1, as amended herein, recites:

> 1. A method of detecting a predisposition to cancer in a human, said method comprising:
> (i) providing a biological sample from said animal;
> (ii) detecting the level of CYP24 nucleic acid or CYP24 protein, within said biological sample, **wherein said CYP24 nucleic acid or CYP24 protein is a nucleic acid or protein encoded by a *CYP24* gene identified in GenBank Accession numbers U60669 or S78775**; and
> (iii) comparing said level of CYP24 nucleic acid or CYP24 protein with a level of CYP24 nucleic acid or CYP24 protein in a control sample taken from a normal, cancer-free tissue; wherein an increased level of CYP24 nucleic acid or CYP24 protein in said biological sample compared to the level of CYP24 nucleic acid or CYP24 protein in said control sample indicates a predisposition to cancer in said animal. [emphasis added]

This claim as amended expressly provides that the nucleic acid or CYP24 protein detected is a CYP24 nucleic acid (*e.g.* CYP24 genomic DNA, CYP24 mRNA) or a CYP24 protein encoded by the CYP24 gene of GenBank listings U60669 or S78775. These listings provide adequate specific sequence information to allow one of ordinary skill to readily detect copy number, mRNA transcription, and protein expression levels fo the subject *CYP24* gene. In addition, the specification expressly provides primers for the detection of gene expression of *CYP24* (see, e.g., Table 1 at page 54). One of skill in the art would readily appreciate that the inventors were "in possession" of methods for detecting copy number, mRNA expression levels, and 25-hydroxyvitamin D3 24-hydroxylase (CYP24 protein) expression levels. Accordingly, Applicants have met the description requirement of 35 U.S.C. §112, first paragraph, and the rejection of claims 1-17 on these grounds should be withdrawn.

35 U.S.C. §112, first paragraph, enablement.

Claims 1-17 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. IN particular, the Examiner alleged that the term "cancer"

encompasses several organ systems with different and distinct histopathologies and various etiologic causative agents. In addition, the Examiner cited Collins *et al.* (1998) *Proc. Natl. Acad. Sci.,* 95: 8703-8708, as allegedly excluding CYP24 as a candidate breast cancer gene. Applicants traverse.

With respect to the Examiner's allegation that the claims read on an inoperable embodiment (breast cancer), Applicants note that the specification expressly states:

> Previously, *CYP24* had been discounted as a candidate oncogene because it was not found to be transcribed in the breast cancer cell line, BT474 (Collins *et al.* (1998) *Proc. Natl. Acad. Sci. USA* 95: 8703-8708). **However, re-evaluation of expression of *CYP24* in cell lines and tumors was warranted because of its position at the peak of the copy number profile and because of the existing knowledge of its function**. Therefore we examined expression levels of *CYP24* and the vitamin D receptor (*VDR*), which controls *CYP24* expression by RT-PCR using the primers listed in Table 1. **This re-evaluation shows that these genes are expressed in breast cancer cell lines and tumors (Figure 3). Expression of *CYP24* and *VDR* was detected in MCF7 cells and higher levels of expression of *CYP24* were induced when cells were treated with 1,25-dihydroxyvitamin-D3 (Figure 3A). Furthermore, expression of *CYP24* and *VDR* was detected in two breast tumors S21 and S59 (Figure 3B)**. [emphasis added] (page 53, lines 11-27).

In addition, the description of the Cancer Program at Cytochroma, Inc. (http://www.cytochroma.com/TACan24.html, attached as Exhibit A) states:

> CYP24 has recently been implicated as an oncogene. In **breast cancer** the CYP24 gene is amplified many fold resulting in a high level of CYP24 expression which may block control of tumor growth normally exerted by calcitriol. **CYP24 activity has been observed to be present and upregulated in seven out of seven different continuous human prostatic carcinoma cell lines examined**. The ability to inhibit the growth of these cell lines is inversely proportional to the level of CYP24 activity in each cell line. In addition, two out of five **non-small cell lung carcinoma cell** lines have been found to express high levels of CYP24. **In non-small cell lung adenocarcinomas, CYP24 has been identified as a gene that is over-expressed in patients with poor survival**.

In addition, Tanaka *et al.* (2004) *Ann. Oncol.,* 15(2): 236-241, implicate CYP24 overexpression in esophageal cancer (*see, e.g.,* Tanaka *et al.* enclosed as Exhibit B).

Elevated CYP24 expression is thus clearly implicated in a number of different cancers. CYP24.

Moreover the Examiner is reminded that the claims only indicate that elevated CYP24 is indicative of a predisposition to cancer, not that elevated CYP24 actually causes the cancer.

In view of the foregoing, Applicants believe the predominant scientific literature supports an association between CYP24 expression and predilection to cancer. Accordingly, Applicants believe the claimed invention meets the requirements of 35 U.S.C. §112, first paragraph, and the rejection of claims 1-17 on these grounds should be withdrawn.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3513.

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